Remarks

Claims 1-30 are pending in the subject application. By this Amendment, applicants have amended claims 1-7, 9-11, and 13-29. Applicants maintain that amended claims 1-7, 9-11, and 13-29 raise no issue of new matter and are fully supported by the specification as filed. Support for amended claim 1 may be found *inter alia* in the specification, as originally filed, on page 4, lines 5-12; and at page 6, lines 15 and 19. Support for amended claim 2 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-15. Support for amended claim 3 may be found *inter alia* in the specification, as originally filed, on page 6, line 16. Support for amended claim 4 may be found *inter alia* in the specification, as originally filed, on page 6, lines 16-17. Support for amended claim 5 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-19. Support for amended claim 6 may be found *inter alia* in the specification, as originally filed, on page 6, lines 20. Support for amended claim 7 may be found *inter alia* in the specification, as originally filed, on page 6, lines 20-21. Support for amended claim 9 may be found *inter alia* in the specification, as originally filed, on page 4, lines 13-21; and page 6, lines 15 and 19. Support for amended claim 10 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-15. Support for amended claim 11 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-19. Support for amended claim 13 may be found *inter alia* in the specification, as originally filed, on page 4, lines 13-21; page 8, line 23 through page 9 line 30; page 15, line 16 through page 16, line 5; and page 6, lines 15 and 19. Support for amended claim 14 may be found *inter alia* in the specification, as originally filed, on page 4, lines 5-13; and page 6, lines 16 and 20. Support of amended claim 15 may be

found *inter alia* in the specification, as originally filed, on page 6, lines 14-17. Support for amended claim 16 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-17. Support for amended claim 17 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-17; and page 7, lines 19-20. Support for amended claim 18 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21. Support of amended claim 19 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21. Support for amended claim 20 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21; and page 7, lines 19-20. Support for amended claim 21 may be found *inter alia* in the specification, as originally filed, on page 6, lines 22-24. Support for amended claim 22 may be found *inter alia* in the specification, as originally filed, on page 4, lines 13-21; page 8, line 23 through page 9 line 30; page 15, line 16 through page 16, line 5; and page 6, lines 15-19. Support for amended claim 23 may be found *inter alia* in the specification, as originally filed, on page 4, lines 5-13. Support of amended claim 24 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-17. Support for amended claim 25 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-17. Support for amended claim 26 may be found *inter alia* in the specification, as originally filed, on page 6, lines 14-17; and page 7, lines 19-20. Support for amended claim 27 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21. Support of amended claim 28 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21. Support for amended claim 29 may be found *inter alia* in the specification, as originally filed, on page 6, lines 18-21; and page 7, lines 19-20. Accordingly, applicants respectfully request entry of this Amendment. Upon entry of this Amendment,

claims 1-30 will be pending and under examination.

Claims Rejected under 35 U.S.C. §112 (Enablement)

In the December 29, 2003 Office Action, the Examiner stated that in response to the rejection of claims 1-12 under 35 U.S.C. §112, first paragraph, as lacking enablement for gene therapy, applicant has amended the claims such that they are limited to treating a genetic disease selected from diabetes, heart disease and cancer. The Examiner stated that first, it must be pointed out that the claims still encompass very broad therapeutic application, and that both heart disease and cancer are broad categories of disease, each of which encompass many disparate conditions having distinct etiology. The Examiner further stated that in the "Remarks", applicant cites three articles to support enablement of the claimed method as it is now limited to treatment of diabetes, heart disease and cancer. The Examiner stated that specifically, Applicant urges that Campbell *et al* (2000) *Cancer Gene Therapy* 7:1270-1278 demonstrate in mice that adenovirus-mediated $p16^{INK4}$ gene transfer significantly suppressed human breast cancer growth. The Examiner also stated that applicant asserts that most of the articles submitted in Paper No. 16 show that gene therapy could be used to treat different types of diseases. The Examiner stated that however, the previous Office Action clearly points out why the vast majority of the art of record fails to provide enablement for gene therapy over any scope. The Examiner stated that furthermore, whatever evidence there might be for enabled gene therapy methods is very limited in scope and does not suggest that therapeutic application of promoters to the treatment of cancer, heart disease and diabetes would be practicable without undue experimentation at the time of filing. The Examiner stated that therefore, for reasons of record and herein above, claims 1-12

stand rejected as lacking an enabling disclosure.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 1 and 9. Applicants note that the claims as hereinabove amended are directed to a method of regulating expression of an exogenous gene introduced into a subject by a gene therapy. To the extent that the Examiner has argued that applicants have not enabled gene therapy, applicants note that the claimed subject matter is not directed to establishing a gene therapy, but instead to regulating expression of an exogenous gene introduced by an extant gene therapy. Accordingly, applicants maintain that the method as claimed is fully enabled by the specification as filed, and request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that claims 1-30 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an expression vector comprising a chimeric regulatory sequence comprising the 900 bp region of the c-myc promoter from -353 to -1257, relative to the transcriptional start site, fused to the first 111 base pairs upstream of the transcription initiation site of the HSP70 promoter and a method of regulating the expression of a nucleic acid in a cell in vitro, does not reasonably provide enablement for any promoter comprising at least one exogenous electromagnetic response element or a method of using the enabled promoter *in vivo*. The Examiner further stated that the claims are directed to promoter constructs, and methods of using said promoter constructs, capable of regulating expression of heterologous nucleic acids in response to electromagnetic field stimulation, wherein the promoters comprise electromagnetic response elements fused to

heterologous regulatory sequences. The Examiner stated that the specification does not set forth any particular structural limitations on electromagnetic response elements. The Examiner stated that, therefore, in the broadest embodiments the claims encompass vectors and methods of using vectors comprising any regulatory element capable of responding to electromagnetic fields The Examiner stated that more narrow embodiments of the claimed invention limit the electromagnetic response elements as comprising an nCTCTn motif.

The Examiner also stated that claims 22-30 are directed to a method for regulating expression of a nucleic acid in a cell using the electromagnetic field responsive promoter. The Examiner stated that according to the broadest reasonable interpretation, the claims encompass a method of regulating expression in vitro or in vivo. The Examiner stated that as the specification provides no asserted utility or guidance as to how the skilled artisan is to use the method in vivo other than gene therapy, the claims lack enablement for the method practiced in vivo for the reasons set forth in previous Office Actions and herein above. The Examiner further stated that with regard to the promoter constructs themselves, the art, like the instant specification, recognizes that a 900 base pair region of the c-myc promoter and a 70 base pair region of the HSP70 promoter are required for electromagnetic field stimulated expression by the native promoters, and that the 900 base pair region from the c-myc promoter can restore the electromagnetic field response when inserted into a HSP70 promoter lacking the endogenous 70 base pair segment required for electromagnetic field stimulation (see, e.g., Blank et al. (2001) J. Cell Biochem. 81:689-692). The Examiner stated that the art further teaches that binding of c-myc to nCTCTn sequences is required for electromagnetic field simulation in the HSP70 promoter (see, e.g., Lin et al. (1998)

J. Cell Biochem. 69:181-188). The Examiner stated that however, although the art has identified certain elements that are required for the electromagnetic response in the c-myc or HSP70 promoters, the art does not define the minimal sequence requirements that confer electromagnetic field responsiveness on any promoter. The Examiner also stated that, that is, the art does not teach what is sufficient to confer electromagnetic responsiveness such that the skilled artisan would be able to make the full scope of any promoter comprising exogenous electromagnetic response elements and capable of electromagnetic field stimulated expression. The Examiner stated that the art generally teaches that the organization of c/s-regulatory elements in promoters is highly complex and integrated. For example, according to the teachings of Arnone et al. (1997) Development 124:1851-1864, the 900 base pair region of the c-myc promoter shown to restore the electromagnetic field response to the HSP70 promoter deletion mutant might be considered a regulatory module. The Examiner stated that Arnone et al. teaches that individual regulatory modules are always found to contain multiple transcription factor target sites, and these contribute in various ways to the overall regulatory output (paragraph bridging pages 1851-1852). The Examiner further stated that, thus, Arnone et al. teaches that it is highly unlikely that a regulatory module could be defined by the binding of c-myc to the sequence nCTCTn, or that the presence of such a sequence would confer electromagnetic field responsiveness to any promoter. The Examiner stated that Lin et al (1998) J. Cell Biochem. 70:297-303 teaches that the complexity of factors participating in the function of expression modules, which Arnone et al. teaches is a general feature of these regulatory elements, is likely also found in the electromagnetic field response. The Examiner stated that Lin et al. states, "[b]ased on the magnetic field-induced binding

activation of both HSF and AP-1, changes in cell behaviour induced by magnetic fields may well result from a combination of the major stress-responsive transcriptional regulatory pathways. The Examiner stated that the multiplicity of elements involved in magnetic field-induced HSP70 transcription could result from intersecting and converging signaling pathways" (paragraph bridging the left and right columns on page 299). The Examiner stated that, furthermore, teachings from the art suggest that the requirements for electromagnetic field responsiveness might not be fully comprised within the 900 base pair segment from the c-myc promoter. The Examiner stated that Arnone et al. teaches that proximal cis-regulatory elements may perform especially important functions in processing the regulatory outputs of more distantly located modules (second full paragraph on page 1856) The Examiner stated that. Lin et al (1999) J. Cell. Biochem. 75:170-176 teaches that the HSP70 response to electromagnetic fields involves the trimerization and binding of HSF1 to a heat shock element in the heat shock regulatory domain of the promoter (right column on page 170). The Examiner also stated that although the specification states, "[t]he electromagnetic field response elements...can be introduced into any gene promoter not having them" (third paragraph on page 3). The Examiner stated that the art is silent with regard to what elements comprised within the 900 base pair fragment of the c-myc promoter are sufficient to confer electromagnetic field responsiveness on any promoter not having an electromagnetic field response element, or whether the 900 base pair fragment would provide electromagnetic field responsiveness in any promoter that does not also comprise the heat shock response element of the HSP70 promoter. The Examiner further stated that as the art teaches that cis-element regulation of gene expression is complex and unpredictable, the skilled artisan is dependent upon the teachings of the specification to set forth

the requirements for an electromagnetic field response element that can be introduced into any promoter not having them such that he can make and use the claimed invention without having to engage in undue experimentation. The Examiner also stated that given the very limited working examples and the complexity of cis-element regulation of gene expression, one of ordinary skill would not know how to make an electromagnetic field response element capable of providing electromagnetic field responsiveness when introduced into any gene promoter not having one. The Examiner stated that therefore, the skilled artisan would have to engage in undue trial and error experimentation to construct a promoter element capable of providing electromagnetic field responsiveness regardless of the surrounding promoter structure. The Examiner stated that furthermore, given that there is no evidence that the 900 base pair myc promoter sequence is operative in any context other than within the c-myc gene or in conjunction with the HSP70 heat shock response element and there is no basis upon which one can predict in which heterologous promoters the 900 base pair fragment would be operative, the skilled artisan would have to engage in undue experimentation to construct and test the 900 base pair fragment with every gene promoter not having an electromagnetic response element to identify those which fall within the scope of the claims. The Examiner stated that for these reasons, making and using any promoter beyond the scope of comprising the 900 bp region of the c-myc promoter from -353 to -1257, relative to the transcriptional start site, fused to the first 111 base pairs upstream of the transcription initiation site of the HSP70 promoter would require undue experimentation.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position,

applicants have hereinabove amended claims 1,9,13, and 22. Initially, applicants note that structural information regarding the EMRE's is provided in claims as hereinabove amended in the form of the widely-accepted description of sequence information, specifically nCTCTn. The Examiner states that Arnone et al. teaches it is "highly unlikely that a regulatory module could be defined by the binding of c-myc to the sequence nCTCTn". In response, applicant initially notes that nCTCTn is not discussed in Arnone et al. Furthermore, applicant notes that Arnone discusses multi-component "regulatory modules" which "contribute in various ways to the overall regulatory output". Applicant notes that this not germane to the claim of an EMRE affecting expression, and more particularly, further notes that the claimed subject matter is not somehow incompatible with the concept of other regulatory elements also affecting such (e.g. in a "regulatory module"). Moreover, applicant disagrees with the Examiner's statement that Arnone et al. teaches "it is highly unlikely that such a sequence would confer electromagnetic field responsiveness to any promoter". Arnone et al. has no teaching with regard to EMRE's, and moreover, nor is there any discussion in Arnone et al. of nCTCTn. Applicants request that the Examiner state the location of the support in the Arnone et al. article for this statement so that they may better address the rejection made.

Applicants further note that with regard to Lin et al., the article is discussing the overall regulatory output and does not in any way teach against the effects of individual regulatory components, such as an EMRE. With regard to this, applicants further note that the claimed subject matter does not recite exclusivity of regulation. Moreover, with respect to the argument that electromagnetic responsiveness may not be

comprised in a segment of a promoter, applicants further note that the claimed subject matter is directed to promoters, and not a 900 base pair *c-myc* promoter segment.

Applicants also note that although some experimentation may be required to identify other promoters falling within the scope of the claims, such experimentation would be standard to one of ordinary skill in the art, and this would not amount to *undue* experimentation. Furthermore, the specification provides the guidance given in the form of, *inter alia*, a working example. Moreover, with respect to the state of the prior art, it is not necessary to delineate all the regulatory elements effects to look at "overall regulatory output" to practice the full scope of the claimed invention, and this is an unduly high burden placed on applicants. In fact, one merely needs to identify electromagnetic responsiveness in a promoter with EMRE inserted (e.g. see claim 1). Applicants further note that, as recited in MPEP §2164.01, the fact that experimentation may be complex does not make it undue, if the art typically engages in such experimentation. Accordingly, applicants maintain that the method as claimed is fully enabled by the specification as filed, and request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected under 35 U.S.C. §112 (Written Description)

The Examiner stated that claims 1-12 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that this is a new matter rejection. The Examiner further stated that the claims have been amended such that they are now drawn to a method of treating diabetes, heart disease or cancer. The Examiner stated that although the disclosure contemplates gene therapy in general, there is no descriptive support for a method

of treating diabetes, heart disease or cancer in the originally filed specification or claims. The Examiner stated that therefore, claims directed to a method of treating diabetes, heart disease or cancer constitute new matter.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 1 and 9. Applicants note that the claims as hereinabove do not recite the claim language referred to by the Examiner as "new matter". Accordingly, applicants maintain that the method as claimed is fully described by the specification as filed, and request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that claims 1-30 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated the claims are directed to promoter constructs, and methods of using said promoter constructs, capable of regulating expression of heterologous nucleic acids in response to electromagnetic field stimulation, wherein the promoters comprise electromagnetic response elements fused to heterologous regulatory sequences. The Examiner stated that the specification does not set forth any particular structural limitations on electromagnetic response elements, and in the broadest embodiments the claims encompass vectors and methods of using vectors comprising any regulatory element capable of responding to electromagnetic fields. The Examiner

stated that more narrow embodiments of the claimed invention limit the electromagnetic response elements as comprising an nCTCTn motif.

The Examiner further stated that the specification provides detailed description of a single species of the promoter of the claimed invention (i.e., a promoter comprising the 900 base pair region from the c-myc promoter inserted into a HSP70 promoter lacking the endogenous 70 base pair segment required for electromagnetic field stimulation). The Examiner stated that with regard to identifying characteristics, the specification teaches that binding of c-myc to nCTCTn sequences is required for electromagnetic field simulation in the HSP70 promoter and that a 70 base pair region of the HSP70 promoter and a 900 base pair region of the c-myc promoter are required for electromagnetic field stimulated expression by the native promoters (Id.). The Examiner stated that the specification does not, however, set forth the elements comprised within a promoter capable of providing electromagnetic field responsiveness to any promoter not having an electromagnetic field response element. The Examiner stated that therefore, the skilled artisan could not possibly envision the full scope of the claimed subject matter based on the teachings of the specification and would not have recognized the that Applicant was in possession of the full scope of the claimed invention at the time of filing. The Examiner stated that although the specification describes an assay by which the skilled might identify the elements comprised by the claimed promoter, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. The Examiner stated that it is not sufficient to define DNA solely by its principal biological property (i.e., it is an

electromagnetic response element) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. The Examiner stated that also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. The Examiner stated that thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. The Examiner stated that rather, it is an attempt to preempt the future before it has arrived. The Examiner stated that with respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention. The Examiner stated that in view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any promoter comprising at least one exogenous electromagnetic response element wherein the promoter is regulated by application of an electromagnetic field. The Examiner stated that therefore, only the described promoter comprising the 900 bp region of the c-myc promoter from -353 to -1257, relative to the transcriptional start site, fused to the first 111 base pairs upstream of the transcription initiation site of the HSP70 promoter meet the written description provision of 35 U.S.C. §112, first paragraph.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 1,9,13, and 22.

Applicants initially note that the claims as hereinabove recite the specific EMRE's present in the promoter, and give the sequence which is readily identifiable (nCTCTn). Moreover, applicants note that a method of modifying a stretch of promoter DNA, wherein the stretch is defined by not containing EMRE's does not require a description of all existing DNAs. One or ordinary skill in the art can readily identify whether a promoter contains EMRE's as set forth in the assay described in the specification and referred to by the Examiner in the Office Action. Furthermore, applicant respectfully notes that they are not claiming DNA's, but merely a method of modifying certain promoters. In addition, applicants note that it is not necessary to fuse the c-myc and HSP70 promoters as suggested by the Examiner (e.g. see page 17, lines 11-13 and 15-17), but these promoters can be electromagnetically responsive with nCTCTn sequences are present (e.g. see page 16, lines 14-15). Accordingly, applicants maintain that the method as claimed is fully described by the specification as filed, and request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected under 35 U.S.C. §112 (Second Paragraph)

The Examiner stated that claims 16, 17 and 19-21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner also stated that the claims are indefinite in the recitation of "the step" in line 1, and that the claims are directed to products and therefore do not comprise steps. The Examiner stated that thus the term lacks antecedent basis.

In response, applicants have hereinabove amended claims 16, 17, and 19-21 to delete the term "step" and recite terms with antecedent basis. Accordingly, applicants respectfully request

that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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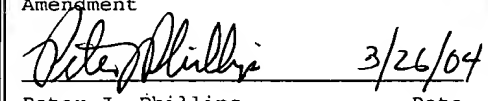
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, Mail Stop Non-Fee Amendment



3/26/04

Peter J. Phillips Date
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